



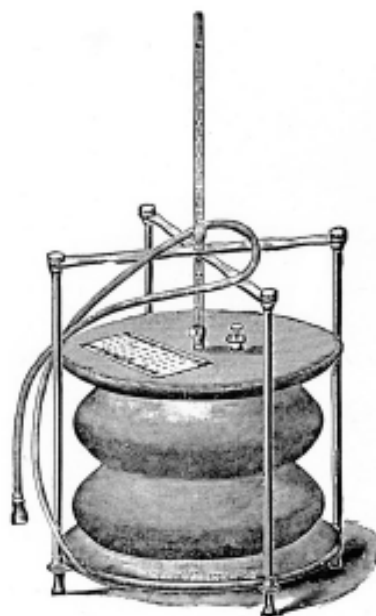
# **Study Specific Spirometry Testing**

**Study AC-060A202 CONTROL**  
**Dorothea Scholl**

Strictly confidential



**AC-060A202 study will use spirometry testing to determine the primary endpoint (FEV1)**



Denison's Spirometer from *Exercise and Food for Pulmonary Invalids*.  
Charles Denison AM MD, Denver: The Chain & Hardy Co.; 1895.  
Courtesy Health Sciences Libraries, University of Washington

## **Pulmonary Function Testing in Clinical Practice vs. Clinical Trials**

- In clinical practice accuracy important but not critical in making a diagnosis
  - combination with history and symptoms
  - looking at trends and general changes
- Clinical trials looks at specific changes and specific changes over time.
  - Accuracy is critical.
  - 50 -100 mL may make a difference in the outcome for a drug
  - 50 -100 mL may be the intra-subject variability at one Visit

## Parameters

- FEV1 (mL)
- FVC (L)
- FEV1/FVC (%)
- PEF (L/sec and L/min (daily peak flow meter))
- FEF25-75% (L/sec)
- Predicted
- % ofP
- Meas (actual)
- % change
- Comp (best test values that will be reported into the database, can come from different efforts)
- B-meas (test from which the FEV1 will be reported)

## Predicted Normal Values

- Quanjer et al, 1993:

Gender	Equation
Male	$4.30 H - 0.029 A - 2.49$
Female	$3.95 H - 0.025 A - 2.60$

H: Standing height (m); A: Age (yr); between 18 and 25 years, substitute 25 years in the equations

- All ethnic groups other than white/caucasian will be race adjusted by a factor conversion factor of 0.9 prior to calculation of FEV1 %oP.

*FEV1 predicted normal (patient of ethnic group other than white/caucasian) = FEV1 predicted normal x 0.9*

## Spirometry Testing in the Study



- **Pre/Post Spirometry testing must be done at all Visits.**
- **Reversibility criteria must be met at visit 1 **OR** 2 (hence the pre/post test is referred to as „Reversibility Testing“ at these visits)**

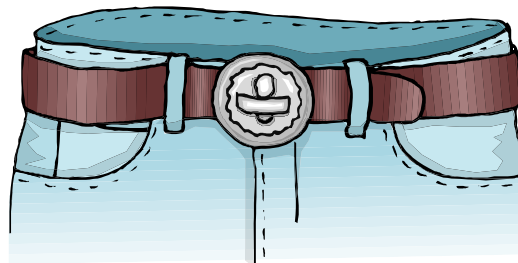
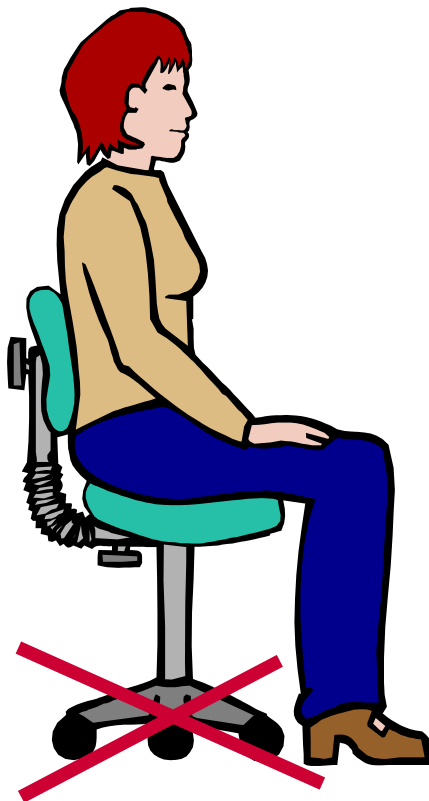
## Avoid the Following Prior to Site Visit:

- Caffeine-containing drinks (1 hr)
- Alcoholic beverages (4 hrs)
- Strenuous exercise (30 minutes)
- Large meals (2 hrs)
- Cold air



**DO NOT TAKE SALBUTAMOL/ALBUTEROL  
FOR 6 HOURS PRIOR TO TEST.**

**If so, please reschedule**





## Performing the Spirometry Test

- Enthusiastic coaching
- Encouragement throughout the test
- Rest between efforts
- Bronchodilator with spacer (wait 15-45 minutes to do post test)
- Repeatable testing between efforts (according to ATS)

## Errors

- Poor effort
- Inconsistent effort
- Coughing
- False start or hesitant start
- Exhalation too short



**Patients that cannot perform acceptable and repeatable tests according to ATS/ERS guidelines should not be enrolled or randomized into the study**

## Assessing the Data



- Minimum 3 efforts
- Maximum 8 efforts
- Acceptable
- Repeatable
- “best”

## Assessing the Data

- After each effort should be assessed if the effort is **acceptable**.
- Discard not acceptable data
  - Still counts as an effort but will not be used in the choice of “best” or “reported” value
- Continue to do another effort until a maximum of 8 efforts or 2 repeatable.
- **Repeatable** Criteria
  - Compare the two tests with the largest FEV1 and FVC
- Report the “best or largest”
  - largest values for the FEV1 and FVC can come different efforts

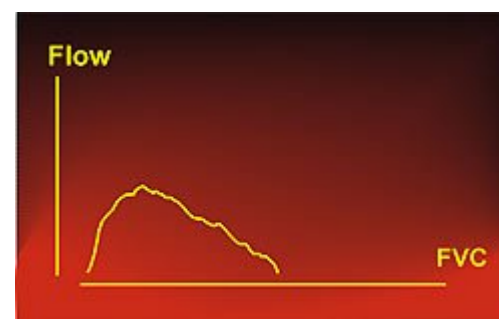
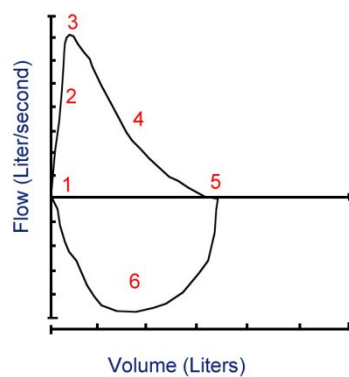
## Acceptable Criteria

- No cough
- Back extrapolation  $< 5\%$  of FVC or 150mL (whichever is greater)
- Minimum 6 seconds exhalation
- Plateau at end of exhalation

## Repeatability Criteria

- Good effort
- Two largest FEV1 within 150 mL
- Two largest FVC within 150 mL
- Two largest PEF within 0.67 L/sec

## Efforts Must Be Maximal



## **“Best” Test / Reported Value for Endpoints**

- Largest FVC
- Largest FEV1
- Largest PEFR
- FEF 25-75% comes from the „best“ (trial with largest sum of FEV1 plus FVC)



## Assessing the Tests

- Investigator to confirm the spirometry results
  - Please ensure that the effort with the “Best” FEV1 is acceptable
    - No coughing, maximal effort, consistent effort, no false start
    - If not acceptable, discard that value and choose a new “Best”



# Reports

## Pre

Subject #: 10001  
 Bender: M  
 Position: Sitting  
 Visit: Visit 3-Week 1 (3)  
 Randomization #:  
 Predicted: ECCS-Actelion  
 First Test: 24/SEP/2010 19:44:51  
 Report Comments: Subject's Reference Value: 2.5\$  
 Stability: PEF % change= 18.9 FEV1 % change= 18.9  
 Baseline Visit Results:

Initials:  
 Age: 20  
 Height: 160.0  
 Interval: Pre FVC (1)  
 Enrollment Code:

Race: Black  
 Date of Birth: 01/JAN/19  
 Weight: 190.0  
 Stage: V3 Pre FVC (1)  
 Tech: rbucha\_sa

Best Test: 24/SEP/2010 19:44:51  
 Last Test: 24/SEP/2010 1

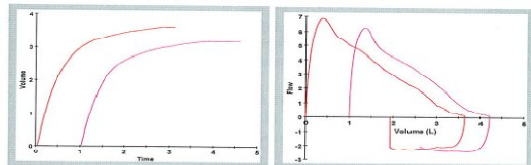
Only on Post

Function	Baseline	Current Best	% Change	ml Difference
FVC (L)	2.95	2.44	-17.29	-510.00
FEV1 (L)	2.38	2.27	-4.62	-110.00
FEV1/FVC (%)	80.68	93.03	15.31	n/a
PEF (L/S)	5.60	5.69	1.61	90.00
FEF25-75% (L/S)	2.12	2.98	40.57	n/a



Actelion Pharmaceuticals Ltd.  
 AC-060A202 (CONTROL)  
 nSpire Site ID: 1  
 PI: No Primary Investigator

Attempts for this Stage: 2. Ranking order: 1,2. Graphs in Rank Order



Authorized Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Repeatability Check NOT Reached.(FVC & FEV1)

Function	Pred	B-Meas	%Prd	Meas	Meas	Meas	Meas	Meas	Meas	Meas
FVC (L)	3.8	3.64	95.8%	3.21						
FEV1 (L)	3.3	3.03	91.8%	2.64						
FEV1/FVC (%)	0.74	0.83	112.2%	0.82						
PEF (L/S)	8.9	6.87	77.2%	6.28						
FEF25-75% (L/S)	4.73	3.03	64.1%	2.70						
VEXT L		0.06		0.05						
VEXT (%)		1.55		1.47						
FLAGS		6SEC BST		6SEC						
EXP TIME		3.13		3.57						

## Inclusion Criteria

- At Visit 1 **AND** Visit 2
  - FEV1  $\leq$  85%
  - No waivers granted if not reached
  - If 85.4% is acceptable as it would be rounded down
  - 85.5% would not be acceptable
- At Visit 1 **OR** Visit 2
  - Post FEV1 Reversibility of 12% **AND** 200 mL
  - 11.5% acceptable 11.4% not
  - 199mL not acceptable

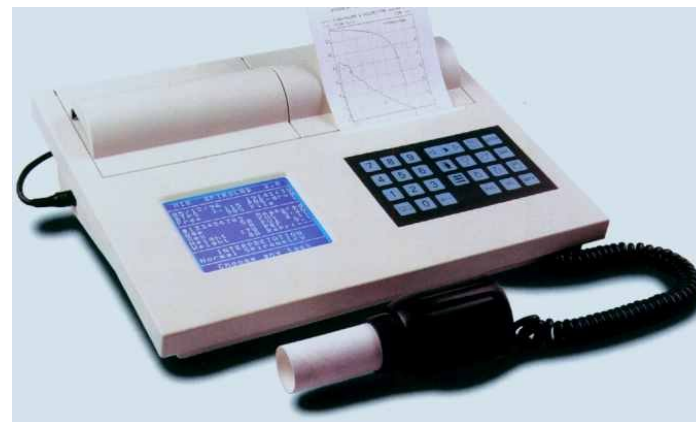
## Peak Exploratory Flow Spirometer vs Daily PiKo



**L/min**

**306**

**Blast out 2-3 sec.**



**L/sec**

**5.1**

**Blast out 6 sec.**

## Reversibility Testing

- Wait 15-45 minutes to perform Post testing
- Must be used for all pre/post (reversibility testing at site
- Patient should use at home
- Patient to bring to each visit



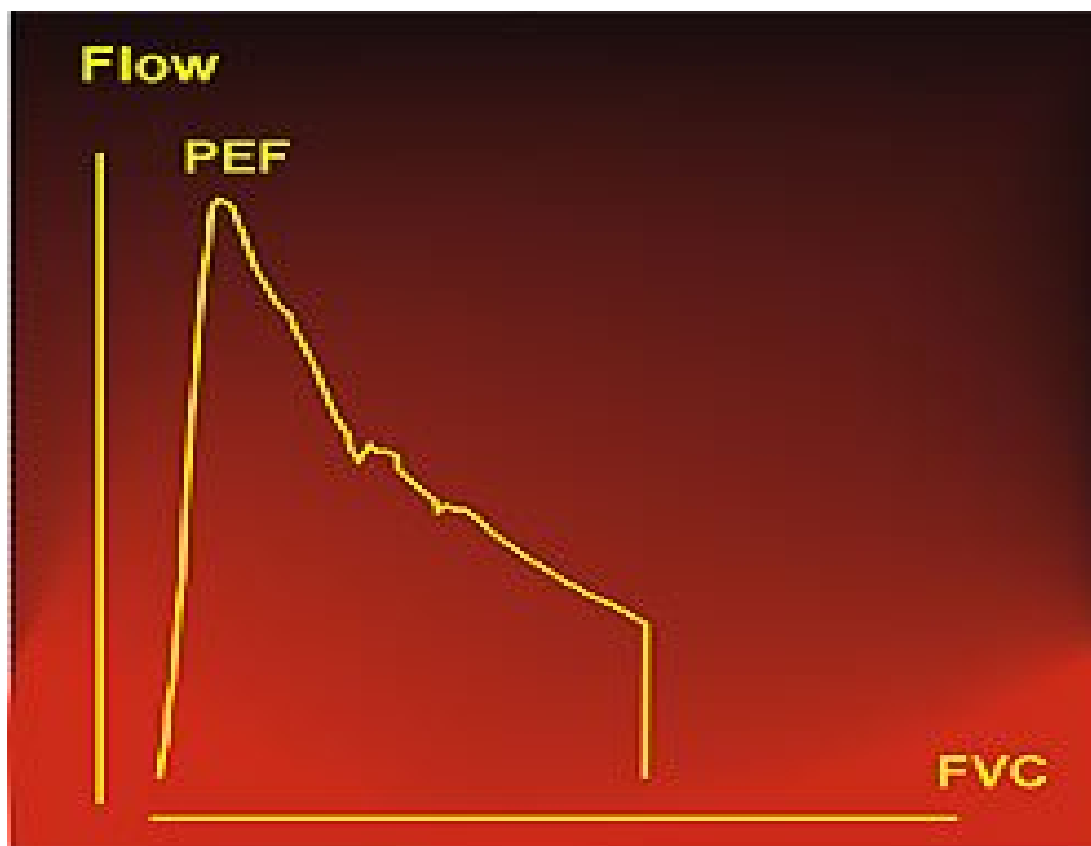
# Spirometry Examples

## Poor Effort



Quanjer et. al. <http://spirxpert.com/characteristic.htm>

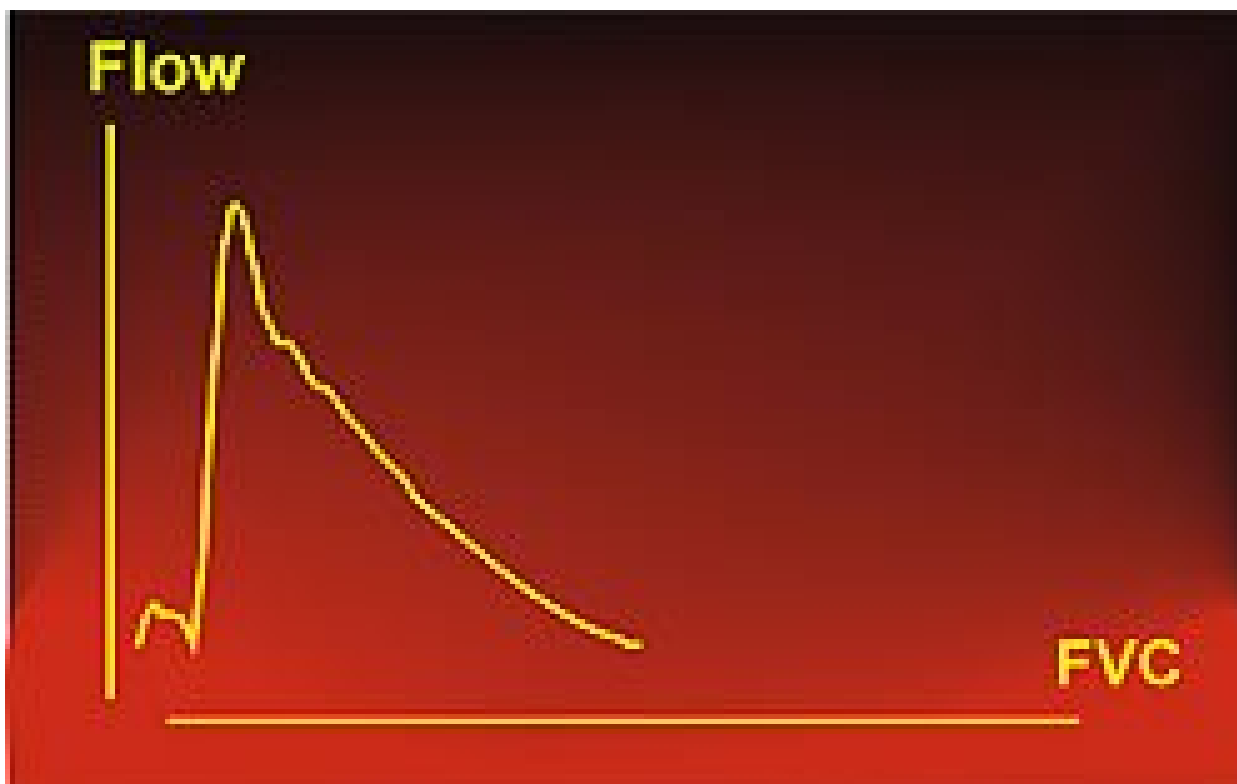
## Premature Termination



Quanjer et. al. <http://spirxpert.com/characteristic.htm>

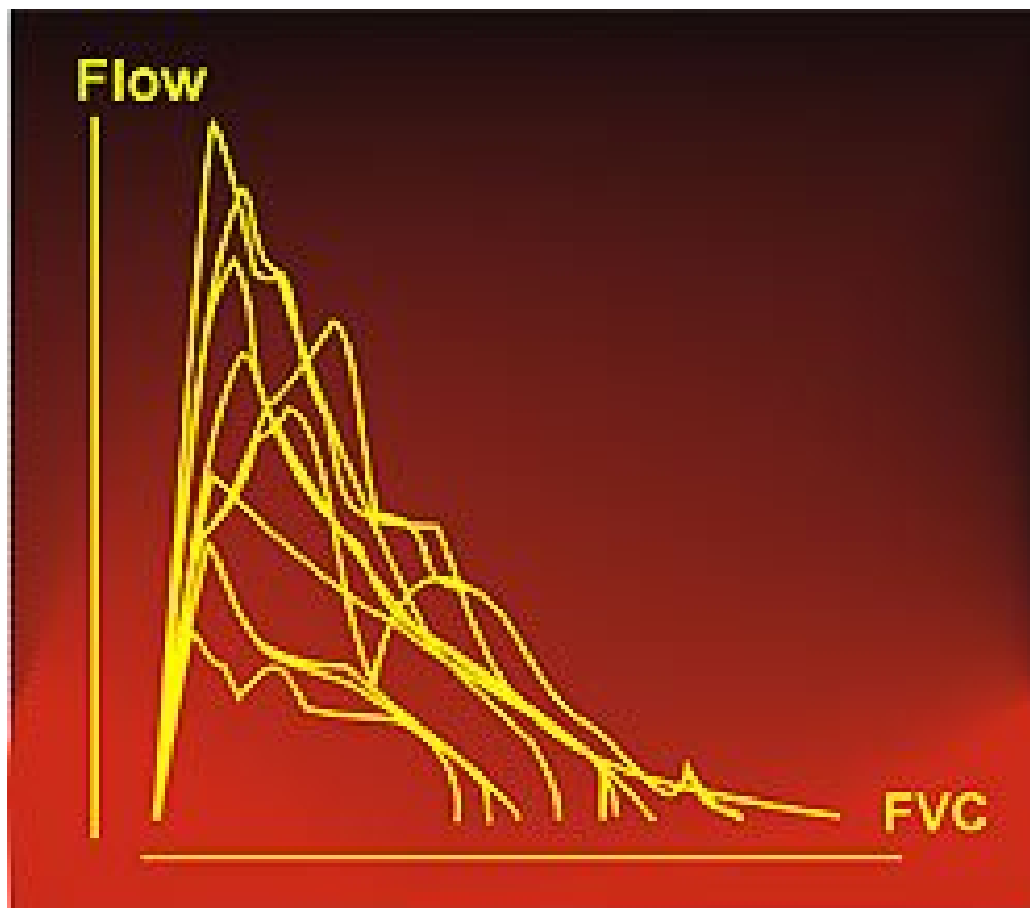


## False Start



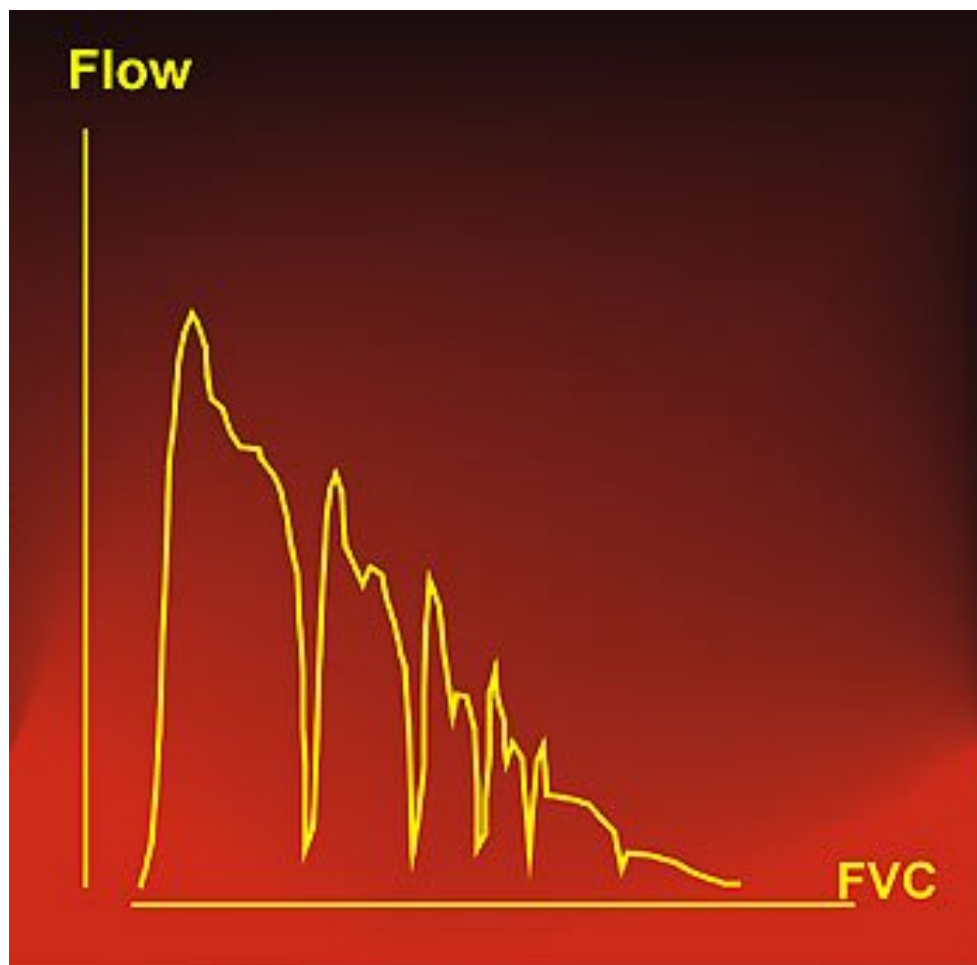
Quanjer et. al. <http://spirxpert.com/characteristic.htm>

## Variable Effort



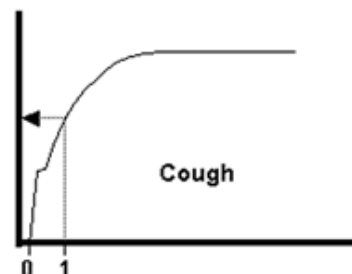
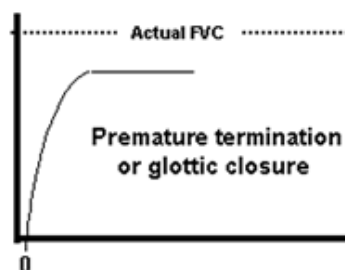
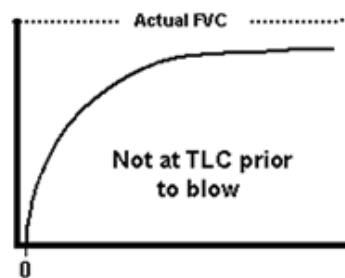
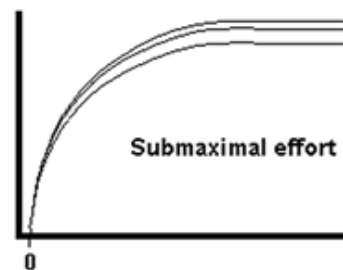
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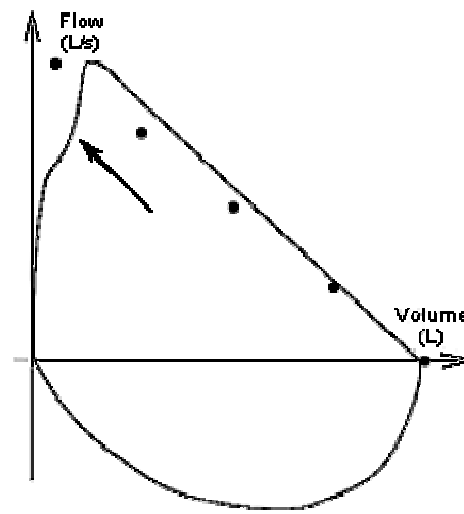
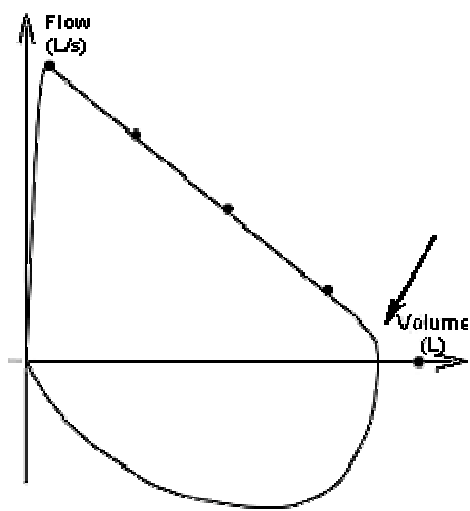
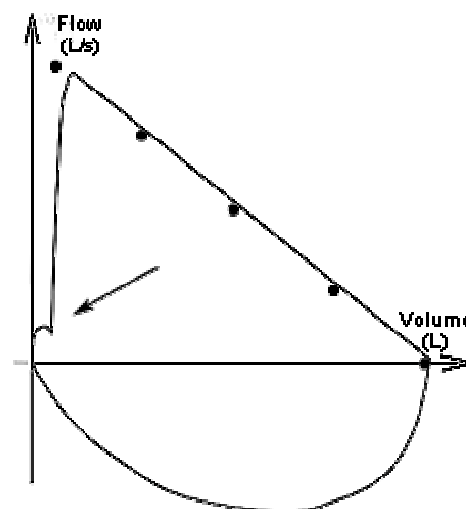
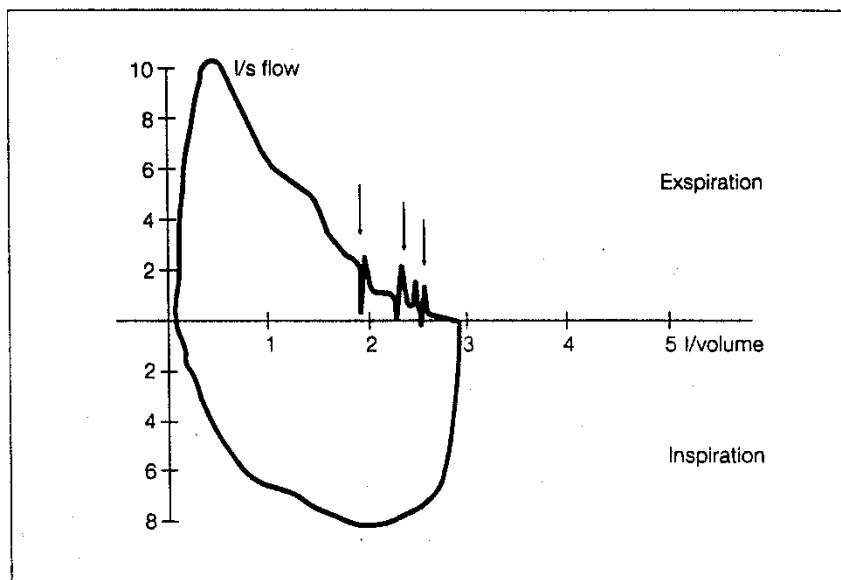
## Cough

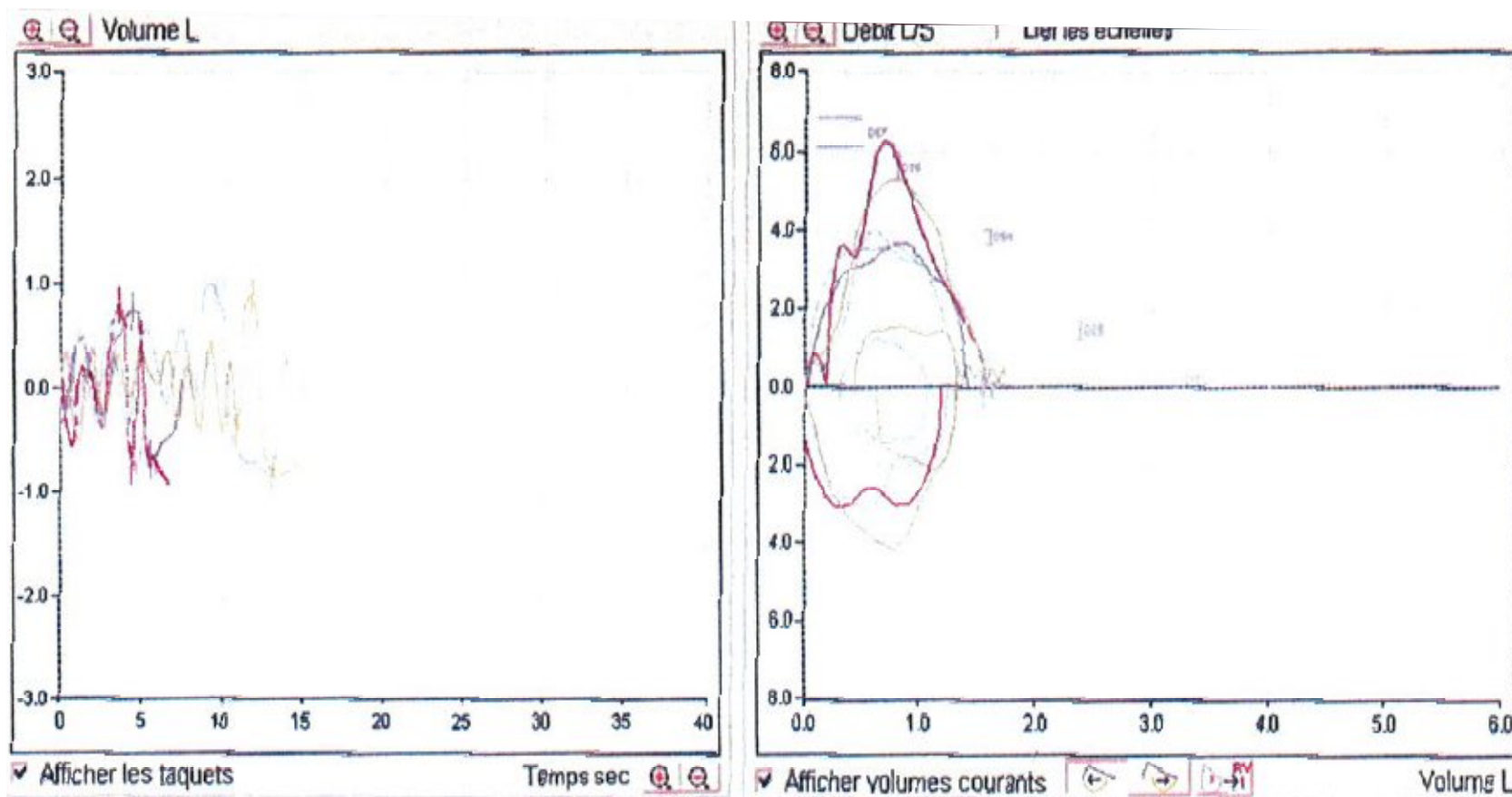


Quanjer et. al. <http://spirxpert.com/characteristic.htm>

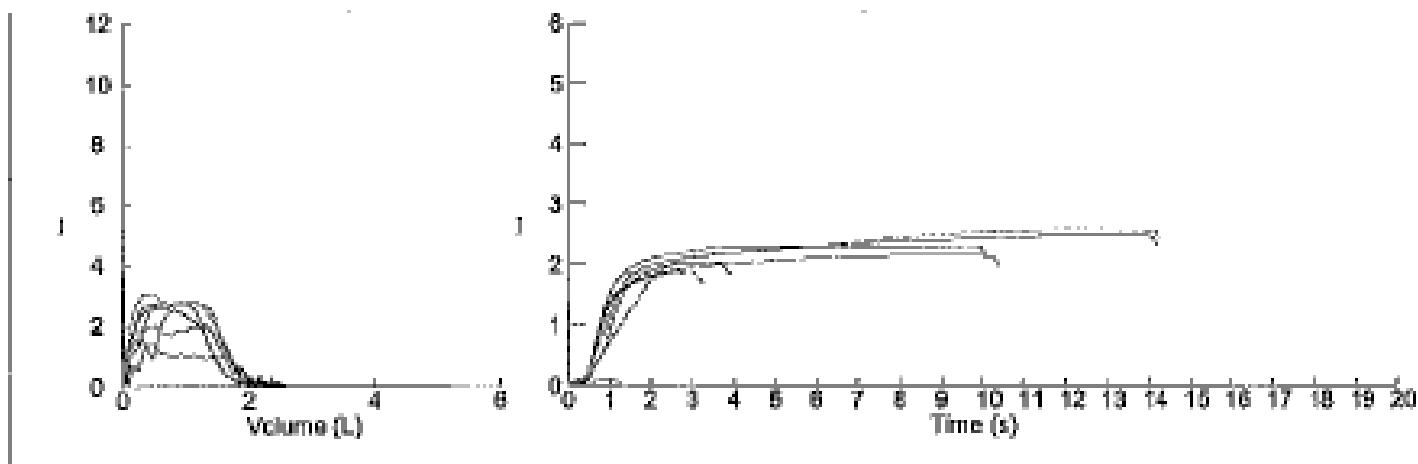
## Within maneuver acceptability criteria







# Submaximal Effort



Reference: Mottram. Mayo Clinic. <http://www.dap.org/CmsFiles/File/Conferences/PFQC%20May%201%20and%202/Presentations/C-Mottram-Spirometry%20QA%20Models.pdf>

## Summary

- Only patients that can do repeatable/acceptable test to be enrolled
- Postpone visit if patient took salbutamol/albuterol within 6 hours prior to schedule spirometry at the visit
- Please use robust coaching techniques
- At Visit 1 do peak flow diary first to set the baseline values
- Salbutamol/albuterol to be given via spacer at each Visit
- Must do post testing within 15-45 minute window
- Encourage spacer use at home
- Examine efforts and discard those that are not acceptable
- Ensure that the “best” test values do not come from unacceptable efforts
- Spirometry alerts (i.e. drop in PEF) are warnings but do not necessitate withdrawal from the study. Please use your clinical judgment whether the patient can continue or not.



## Standards/Guidelines

- ATS Guidelines  
<http://thoracic.org/statements/>
- ERS  
[http://www.ersnet.org/4/1/4\\_1.asp](http://www.ersnet.org/4/1/4_1.asp)
- Global Initiative for Asthma (Gina)  
<http://www.ginasthma.com/>

*The achievements of an organization are the  
results of a combined effort of each  
individual*

*Vincent Lombardi*



**Thank you for your efforts  
and  
all the best!!**